ORGANIZATIONAL OVERVIEWS

OFFICE OF THE DIRECTOR

During the past several years, the program responsibilities of NIAID have increased in scope and complexity, most notably in biodefense research, international presence, and preparations for the possibility of pandemic influenza. To address these changing needs and to improve the efficiency of the operations of the NIAID Office of the Director (OD), the Institute has significantly reorganized the OD offices. The new infrastructure and more strategically defined roles and responsibilities will maximize the ability of NIAID to achieve its mission to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. The process of reorganizing OD offices began in 2004; the new office structure took effect in April 2006. Additional changes will be announced as they become official.

The NIAID OD provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. OD is the chief liaison with the Director of NIH, other components of the Department of Health and Human Services (DHHS), other Federal agencies, Congress, professional societies, voluntary health organizations, and additional public groups. The activities of OD include advising and guiding the NIAID leadership on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs. Offices within OD provide critical management and administrative support to the Institute. By carrying out their individual tasks, OD offices play key roles in helping the Institute achieve its mission. Brief descriptions of OD offices follow.

The **Office of the Chief of Staff for the Immediate Office of the Director** manages and directs executive-level activities, functions, and priority-setting for all tasks occurring within the Immediate Office of the Director (IOD), NIAID. IOD manages critical points of contact and related information flow to resolve and respond to external inquiries involving trans-NIAID and trans-NIH research issues. IOD addresses the political and cultural implications of current research and the initiation or expansion of research in specific areas by coordinating communications with outside lay, professional, and other organizations; brings the perspective of the NIAID Director to the development of NIAID program goals and objectives; advises and assists the Director, the Deputy Directors, and other key officials on all aspects of the mission, activities, and functions of the IOD; and is responsible for overseeing the effective and efficient planning and coordination of executive operations within the IOD.

The **Office of Management and Operations (OMO)** provides mission- and values-based business leadership, direction, support, and assistance to NIAID's national and international programs and activities. OMO oversees and directs the business management and administrative functions of the Institute, government relations and public communications, coordination of the Institute's global research effort, technology development, biodefense research, and policies and procedures for business and program management activities. OMO maintains liaison with and represents the Institute to NIH and DHHS officials and is responsible for the leadership and policy direction of overall program support and business management functions.

OMO directs and coordinates the activities of the following offices and operations:

- The **Office of Administrative Services (OAS)** directs, coordinates, and conducts specific administrative activities of the Institute. OAS advises the Director and senior staff on program management

and develops administrative policies and procedures.

OAS directs and coordinates the activities of the following branches and operations:

- The **Extramural Administrative Management Branch (EAMB)** advises the staff of the extramural programs on administrative policies and practices, and provides administrative support services to the extramural programs. EAMB analyzes the effects of changes in administrative policies and practices by organizational levels above NIAID, apprises the Deputy Director for Science Management of these effects, and helps coordinate the handling of administrative or management problems that cross program lines and cannot be resolved at the program level.

- The **Intramural Administrative Management Branch (IAMB)** coordinates the handling of all administrative, management, and facility support problems associated with the Division of Intramural Research (DIR). IAMB advises the staff of the DIR Director and other key officials about administrative policies and practices and provides overall administrative support services to DIR.

- The **Management Services Branch (MSB)** advises the NIAID Director and other senior staff on general management, administrative issues, and policies for the Institute. MSB develops, implements, and provides advice on regulations, policies, and procedures for the Institute; prepares staff papers and reports on general management issues; and analyzes the effects of changes in administrative policies and practices by organizational levels above NIAID. MSB provides general administrative and support services for OD, provides foreign travel processing services to OD, and designs and conducts management studies and surveys.

- The **Office of Biodefense Research (OBR)** plans, coordinates, implements, and supports the biodefense research efforts of NIAID, including critical research to develop medical countermeasures against biological, radiological/nuclear, and chemical threats. OBR also executes the Trans-NIH Intramural Biodefense Research Program, and coordinates biodefense and biodefense-related research issues across NIH through committees such as the NIH Biodefense Research Coordinating Committee. OBR disseminates information on the Institute's biodefense research programs, policies, and funding opportunities, and interacts with DHHS and other Federal agencies on many biodefense and security issues.

- The **Office of Communications and Government Relations (OCGR)** oversees efforts to interpret and disseminate the goals and results of NIAID research programs and projects to all its constituents, including the biomedical community, Congress, the media, specialized groups, physicians and healthcare providers, other federal agencies, and the general public at national and international levels. OCGR develops the Institute's short- and long-term communications policies, goals, objectives, and strategies; serves as the liaison and point of contact for all legislative matters; coordinates responses to all NIAID-directed media inquiries; and writes news releases, Web content, and statements directed to the media. These include requests for information and records submitted under the Freedom of Information Act (FOIA) and Privacy Act (PA) programs. OCGR writes the content for many NIAID print publications and the NIAID Web site,

manages the Web site, and serves as the Institute's liaison with appropriate voluntary, advocacy, and professional societies.

OCGR directs and coordinates the activities of the following offices and operations.

- The **Digital Policy and Information Office** oversees the Institute's Web policy, content, and standards.
- The **Freedom of Information Office** responds to requests for information submitted under the FOIA and PA programs.
- The **Office of Global Research (OGR)** provides coordination of NIAID's international activities through a matrix of international liaisons. OGR stimulates new initiatives in international research and assists in planning for international programs. Such programs include collaborative international research programs on selected infectious diseases of substantial health importance in developing countries, as well as NIAID intramural and extramural worldwide biomedical research on infectious and immunological diseases. OGR helps stimulate communication across the Institute on international matters, provides technical support to NIAID international research projects and staff assigned overseas, and functions as the liaison with the Fogarty International Center and other relevant international programs within NIH and with other Federal entities. OGR maintains comprehensive knowledge of and information for the NIAID international research portfolio.
- The **Legislative Affairs and Correspondence Management Branch (LACMB)** responds to congressional and public inquiries. LACMB prepares congressional briefings, testimony, and reports, analyzes legislation, and assists with correspondence and other requests for information from the NIH Executive Secretariat.
- The **News and Public Information Branch (NPIB)** coordinates responses to media calls and writes and disseminates news releases, Web pages, and other resources for the media. NPIB staff members also develop and disseminate pamphlets, fact sheets, and other public information materials; coordinate logistics for NIAID lectures, exhibits, and other special events; oversee the NPIB support contract; and coordinate public liaison and selected outreach activities.

- The **Office of Ethics (OE)** administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public. OE develops and recommends policies and procedures related to employee standards of conduct, financial interests and disclosure, and outside activities. OE reviews and approves financial disclosure reports and requests for outside activities, maintains all records associated with its ethics functions, and provides advice and assistance to employees regarding the application of the ethics laws, regulations, and policies. In addition, OE provides ethics training, serves as the NIAID liaison for ethics issues to the DHHS Office of the General Counsel and the Office of Government Ethics, and provides advice to OD.
- The **Office of Strategic Planning and Financial Management (OSPFM)** directs and coordinates the Institute's strategic planning and evaluation activities, integration of long-term financial and capital asset resource requirements, budgeting, financial management activities, and knowledge management. In collaboration with members

of the Institute's scientific Divisions and executive management, OSPFM develops, directs, and coordinates strategic plans, policies, goals, objectives, strategies, and techniques in support of the Institute's missions. OSPFM serves as liaison for all trans-NIAID planning and financial management activities and works with the NIH Office of the Director to ensure that the Institute has a long-range, sustainable vision and program plan for carrying out its mandate.

OSPFM directs and coordinates the activities of the following offices, branches, and operations.

- The **Knowledge Management Office (KMO)** serves the executive officers of OMO and their staffs by arranging access and delivery of information critical to the daily operations of NIAID. Together with other OMO offices, the KMO manages access, planning, and infrastructure for knowledge repositories and assets. The KMO also arranges for the ongoing management and oversight of the Institute's knowledge assets as they apply to OSPFM functions.

- The **Budget and Financial Management Branch (BFMB)** formulates, presents, and executes budgets for the $1.5 billion AIDS program, the $1.6 billion biodefense program, and the $1.3 billion immunologic and infectious diseases program. BFMB analyzes, reviews, and approves grant financial plans, and develops financial content and data management tools.

- The **Mission Planning and Integration Branch (MPIB)** translates research actions and agendas to project long-term financial and capital asset needs, including human capital, and to develop integrated long-range mission plans. MPIB also conducts long-range statistical analyses and modeling to support scientific program operations and initiatives and to inform decision making.

- The **Strategic Planning and Evaluation Branch (SPEB)** provides institutional leadership for trans-NIAID strategic planning, and conducts assessments of research programs and recommends subsequent activities. SPEB determines and updates information about the state of science and emerging scientific opportunities and barriers.

- The **Office of Technology Development (OTD)** supports NIAID's intramural and extramural research programs by facilitating collaborations between NIAID researchers and external research and development organizations. OTD's staff utilizes scientific, legal, and business expertise to negotiate agreements with universities, small biotechnology companies, large national and multinational pharmaceutical companies, and other government agencies. OTD manages NIAID's portfolio of patents and inventions and serves as NIAID's resource for all issues concerning intellectual property. OTD facilitates receipt of Cooperative Research and Development Agreement funds, supports NIH's licensing program, tracks license royalty receipts, and provides NIAID investigators with training on NIH technology transfer policies and regulations. OTD coordinates NIAID's interactions with NIH's other Institutes and Centers on technology transfer issues, and is an active participant in many committees that develop and implement NIH technology transfer policy.

- The **Offices of Chief Information Officer and Technology Information Systems** include the Office of the NIAID Chief

Information Officer (OCIO) and the Office of Technology Information Systems (OTIS). OCIO provides leadership and direction of effective strategies, policies, executive responsibilities, and standards for technology services; support for biomedical research programs; and administration of information technology resources. These activities are crucial to the broadened, expanded, and intensified role of technology in support of NIAID's mission. The CIO is also the Director of the Office of Technology Information Systems.

OTIS manages and administers technologies that support NIAID biomedical research programs. The Office provides a spectrum of management, technologies development, applications/software engineering, bioinformatics support, and professional development. OTIS works closely with NIAID intramural, extramural, and administrative staff to provide technical support, liaison, coordination, and consultation on a wide variety of ventures. These projects and initiatives are aimed at ensuring ever-increasing interchange and dissemination of scientific information within the Federal government and among NIAID-supported biomedical researchers worldwide.

OTIS directs and coordinates the activities of the following branches and programs:

- The **Bioinformatics and Scientific IT Program (BSIP)** provides leadership in fields related to bioinformatics, with special emphasis on NIAID needs and requirements. This program helps coordinate scientific and technological expertise for planning, forming partnerships with researchers, and assisting with lab projects. Specific emphasis areas include high-performance super-computer cluster resources and biocomputing consulting involving structural biology, phylogenetics, and biostatistics.

- The **Scientific Applications and Information Systems Branch (SAISB)** provides core cyber technologies research, development, and engineering of applications in support of NIAID biomedical research. SAISB services include formulating, designing, developing, implementing, executing, maintaining, and evaluating technology including applications, services, and systems. Using contemporary management standards and best practices, analysts and information technology developers respond to researcher and administrator requests. These activities involve the management of software, systems, and applications.

- The **Extramural Services Branch (ESB)** provides cyber technologies technical management and support for the Institute's extramural biomedical research program administration, including support to off-campus administrative offices, extramural biodefense research, and allied programs. ESB manages operational testing, implementation, technical maintenance, security, and user support for applications and systems employed in research program administration. ESB provides essential services to facilitate local area network/wide area network (LAN/WAN) connectivity, NIAID telework, and a collegial, authorized, and accessible framework for automated information sharing and collaboration.

- The **Intramural Services Branch (ISB)** provides technical management and support for the cyber technologies used in NIAID intramural biomedical research programs, including technology support

to intramural biodefense research. ISB's activities on behalf of the intramural research community parallel those of ESB for the extramural research community. In addition, ISB supports the Rocky Mountain Laboratories and NIAID programs at Fort Detrick, Maryland, and other continental U.S. operations.

- The **Policy and Resources Management Branch (PRMB)** is responsible for oversight, policy, and guidance of cyber technology programs throughout NIAID. PRMB provides coordination for technology-related policy, strategic planning, capital planning and investment control, governance, technology acquisitions, administration, and alignment of resource administration with NIAID biomedical technologies programs. PRMB enhances human resources professional development through inservice training, professional development activity in the laboratories, and collaboration with interdisciplinary professionals.

- The **Office of Workforce Effectiveness and Resources (OWER)** advises the leadership of NIAID on organizational performance, effectiveness, and efficiency. OWER conducts human capital oversight, including Title 42, Title 5, and performance management; workforce planning; recruitment; and paid advertising. OWER also oversees learning and development programs for the Institute and facilitates internal communications, including OD/DIR Intranet development and newsletters.

  OWER directs and coordinates the activities of the following branches:

  - The **Workforce Management Resources Branch (WMRB)** assists NIAID senior managers in assessing organizational and programmatic human capital requirements. WMRB helps broker and implement human capital solutions for the NIH Office of Human Resources and other appropriate offices and staff.

  - The **Workforce Retention and Development Branch (WRDB)** advises NIAID senior leadership on ways to measure the success of the organizational structure and assists senior managers in the areas of learning, development, and change management to enhance overall organizational capability and talent development. WRDB provides leadership, oversight, and guidance for learning and development initiatives, including business process improvement and internal Institute communications.

- The **Division of Clinical Research** replaces the Office of Clinical Research, formerly a component of the OD. A description of the newly established Division will appear in the FY 2006 Profile.

OUTREACH ACTIVITIES

An important part of NIAID's mission is to disseminate research results to the media, health professionals, and the general public and to recruit volunteers into clinical trials of potential disease treatment and prevention methods. Several NIAID divisions and offices initiate and participate in targeted outreach activities. These activities include producing and disseminating print, audiovisual, and Web-based materials; distributing materials at professional and community meetings; and sponsoring workshops, seminars, and conferences for the media, health professionals, researchers, and the general public.

In FY 2005, the NIAID Office of Communications and Public Liaison (OCPL), renamed the News and Public Information Branch, produced materials on allergic, immunologic, and infectious diseases as well as potential illnesses caused by agents of bioterrorism. The NIAID Web site, which is visited approximately 800,000 times each month, contains a wealth of information about NIAID's organization, laboratories, and research programs. It also contains health information on many NIAID research topics. Web users looking for health information can download and/or request NIAID printed materials. *(www.niaid.nih.gov)*

In FY 2005, OCPL published two new health information products, available in print and online: Tuberculosis: Getting Healthy and Staying Healthy (*http://www.niaid.nih.gov/publications/tb.htm*) and Is It a Cold or an Allergy? (*http://www.niaid.nih.gov/publications/flu.htm*). Both are also available in Spanish.

Scientific and health-related meetings are important vehicles for OCPL's outreach efforts. Institute staff members distribute materials and answer questions about NIAID research, training, and job opportunities at conferences, including those sponsored by the American Academy of Allergy, Asthma and Immunology; American Society for Microbiology; Infectious Diseases Society of America; and Annual Biomedical Research Conference for Minority Students.

An OCPL communications initiative continues to expand Institute efforts to keep hundreds of voluntary and scientific organizations updated about Institute activities. Periodic e-mails provide timely news on NIAID research advances that relate to the specific research interests of each organization. In addition, OCPL disseminates NIAID news through the *NIH Public Bulletin* (*http://getinvolved.nih.gov/newsbulletins.asp*).

OCPL is involved in outreach activities related to the construction of several NIAID-funded biosafety laboratories. Most prominent among these activities is the neighbor outreach program in Hamilton, Montana, where construction of a new Integrated Research Facility is under way at NIAID's Rocky Mountain Laboratories (RML). RML has established a database of about 200 RML neighbors it can contact rapidly about ongoing RML activities, including new construction.

In October 2004, RML began distributing a monthly laboratory construction bulletin. In addition, RML staff participate in monthly construction meetings with neighbors and interested parties, and the RML Community Liaison Group meets quarterly and receives both scientific and RML development planning updates.

In FY 2005, RML coordinated two informational symposia for the community—one on pandemic influenza and the other on chronic wasting disease in elk and deer. The symposia combined the talents of State and local health experts and NIAID researchers from RML and Bethesda, Maryland, who presented information to the community and answered questions. RML also collaborated with the State public health agency to share a video of the pandemic influenza symposium with more than 50 county and

tribal health offices. A DVD of the influenza symposium was sent to the Montana Department of Public Health and Human Services to circulate to about 50 of its health jurisdictions.

In four local middle schools, RML sponsors a scientific educational program for children called "Biomedical Research After School Scholars," or BRASS. RML displays information about its scientific mission and research in staffed booths during the Ravalli County Fair and the Bitterroot Spring Fair. Laboratory staff members give facility tours to numerous local, State, and international groups.

Through its Division of AIDS, NIAID is actively involved in educating the public about HIV vaccine research. Targeting at-risk populations, particularly African-Americans, Hispanics/Latinos, and men who have sex with men (MSM), NIAID is implementing a national education campaign to increase awareness of and support for HIV vaccine research. Specifically, the campaign is designed to

- increase awareness about the urgent need for an HIV vaccine;
- create a supportive climate for current and future HIV vaccine trial volunteers; and
- improve public perceptions and attitudes toward HIV vaccine research.

NIAID also sponsors the Community Education and Outreach Partnership Program (CEOPP). This program is designed to increase the capacity of organizations to conduct awareness and educational activities that will increase knowledge and awareness about HIV vaccine research in their targeted at-risk communities, and to foster more positive attitudes about HIV vaccine research so that communities are more supportive of and receptive to volunteering for HIV vaccine trials. In 2004, eight awards were made to national organizations and 20 were made to local community-based organizations (CBOs).

In 2005, 14 additional awards were made to CBOs located in areas where NIAID conducts HIV vaccine research. These CEOPP awardees partnered with local NIAID-sponsored HIV Vaccine Trial Units and NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC) to strengthen collaborative efforts and build capacity of CBOs to conduct HIV vaccine awareness and education activities.

Through its HIV vaccine education campaign, NIAID conducted a national survey in which attitudes and knowledge about HIV vaccine research were evaluated in the general population as well as in segmented groups of African-Americans, Hispanics/Latinos, and MSM. Results of the survey show that misinformation and distrust continue to present formidable barriers to supporting HIV vaccine research, and that low public awareness and knowledge of HIV vaccine research must be addressed to develop and sustain HIV vaccine clinical research efforts. NIAID staff used the research findings to identify key messages and formulate a campaign strategy that would be both effective and powerful. Key messages include:

- No HIV preventive vaccine is available currently;
- Only HIV-negative individuals may participate in HIV preventive vaccine trials;
- No one can get HIV from the vaccines being tested;
- Volunteers from all populations must participate in clinical trials to develop an HIV vaccine that works in each population; and
- HIV vaccines are our best hope to end the HIV pandemic.

Another major HVCC activity is coordinating activities for the annual HIV Vaccine Awareness Day (HVAD) on May 18th. HVAD was

established as a day to acknowledge and thank volunteers and researchers involved in HIV vaccine research. Community activities and media events around the country highlight research advances, address challenges associated with HIV/AIDS, and recognize volunteers who have participated in HIV vaccine clinical trials. (See page 21 for more information.)

The VRC is dedicated to basic and clinical research on the development of vaccines against HIV/AIDS and other human diseases. The VRC recruitment and outreach team is charged with the recruitment and retention of prospective volunteers into vaccine trials, production and dissemination of educational materials, and outreach to all communities, with special attention to those communities most affected by the HIV pandemic and other emerging and re-emerging infectious diseases (e.g., Ebola, West Nile virus, severe acute respiratory syndrome or SARS, etc.).

The team, which consists of two outreach coordinators and a molecular biologist, works closely with CBOs, AIDS service organizations, high schools, universities, churches, and medical establishments to increase awareness and educate the public about HIV vaccine research. The team participates in various community events, visits local and national organizations, gives presentations, and invites groups and individuals to the Center for a first-hand look. The VRC is currently supporting the Capital Area Vaccine Effort (CAVE) and the Community Education Group (CEG). CAVE/CAB, a community advisory board, devises strategies to harness the power of people as educators, watchdogs, and advocates for volunteerism, activism, testing, and research for HIV vaccines. CEG provides information about clinical trials to minority communities, using small groups to explain how clinical trials work and why it is important for minority communities to get involved. CEG is a 2005 CEOPP awardee and has diligently integrated preventive HIV vaccine research into its program. Both organizations work closely with the VRC's recruitment and outreach team and have been instrumental in providing advocacy and disseminating information about HIV vaccines.

The recruitment team along with the clinical team strives to foster positive relationships in order to build trusted and productive community partnerships. OCPL has collaborated with the team in outreach efforts by proposing volunteer stories to local news media, helping develop marketing campaigns, and coordinating the development of informational materials for use by the VRC and the NIAID-supported HIV Vaccine Trials Network. Increasing public awareness and education are essential to sustaining clinical trial enrollment and cohort diversity. They are important factors in increasing public involvement with all aspects of HIV vaccine development and approval. Additionally, enhanced public awareness and education are of paramount importance in communities most affected by HIV.

RESEARCH PLANNING

NIAID's long-standing tradition of rigorous research planning depends on the development and prioritization of specific research initiatives on an annual basis and on long-range strategic planning. NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report, *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health*. The research planning process derives much of its strength from two planning events, the annual Winter Program Review and the Summer Policy Retreat.

Winter Program Reviews

NIAID's annual program reviews bring Institute scientists and senior staff together to focus on future research opportunities and to review proposed research initiatives for new and ongoing research programs.

The specific objectives of the annual program reviews are to

- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;
- Enable NIAID leaders to discuss the scientific framework for and priority of new and ongoing research programs in the context of the above factors; and
- Provide information useful in making decisions about research activities and initiatives to be implemented in the future budget year.

Summer Policy Retreats

Annual policy retreats further enrich the planning process by providing decisionmakers with opportunities to

- Focus on broad scientific issues, opportunities, gaps, and directions;
- Identify scientific opportunities and gaps;
- Ensure that scientific planning addresses the interests and priorities of the Congress, the Administration, the Department of Health and Human Services (DHHS), and the NIH Director;
- Propose ways to respond to newly identified opportunities and needs;
- Explore the implications of changes in scientific or programmatic direction; and
- Set priorities for newly identified opportunities and needs within future budget years.

Each year, NIAID convenes scientific workshops, program reviews, and blue ribbon panels to evaluate progress and to determine future needs and opportunities for the many diseases and areas of research within the Institute's purview. The NIAID Director and each research division consult extensively with NIAID stakeholders, a diverse group that includes scientific experts, professional societies, and patient advocacy groups, and work with them to develop long-range strategic plans as well as specific research initiatives. Areas of emphasis articulated in strategic plans, as well as those identified by DHHS, NIH, Congress, the White House, and others, also help shape the Institute's decision-making and priority-setting process for new and continuing research programs.

Planning for future research initiatives is a multistep process that begins 2 years in advance of the projected implementation date. Throughout the process, the concepts for research initiatives are reviewed and refined. Concepts are first discussed internally during the annual program review, and undergo a second level of review and clearance by the National Advisory Allergy and Infectious Diseases Council. NIAID staff members then develop approved concepts into various forms of grant and contract solicitations,

which are announced to the scientific community. Proposed research projects are peer-reviewed and awarded on the basis of scientific merit, program relevance, and need.

Strategic Planning

In 2000, NIAID developed a comprehensive strategic plan, *NIAID: Planning for the 21st Century,* which grew out of an intensive effort that included a task force of national experts. The plan described broad-based priorities to guide NIAID programs, policies, and initiatives through the next 3 to 5 years. The full text of the plan can be accessed at *www.niaid.nih.gov/strategicplan.*

Since completing the strategic plan, NIAID has extended its reach through specific planning documents. The NIAID guiding principles for global health research are articulated in the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis.* This plan identifies short-term, intermediate, and long-term research goals to address these devastating international killers. The plan can be accessed at *www.niaid.nih.gov/publications/globalplan.htm.*

NIAID has also defined its major and growing program for biodefense research through a series of plans and agendas based on expert recommendations and an intricate strategic planning process. The biodefense program was spurred by the anthrax mail attacks of 2001. In 2002, NIAID convened the first Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research to assist in developing the *NIAID Strategic Plan for Biodefense Research,* the *NIAID Biodefense Research Agenda for CDC Category A Agents,* and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens.* In 2005, NIH issued the *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats.* This plan builds upon and extends NIAID's activities in the biodefense arena and can be accessed at *http://www3.niaid.nih.gov/about/overview/planningpriorities/RadNuc_StrategicPlan.pdf.*

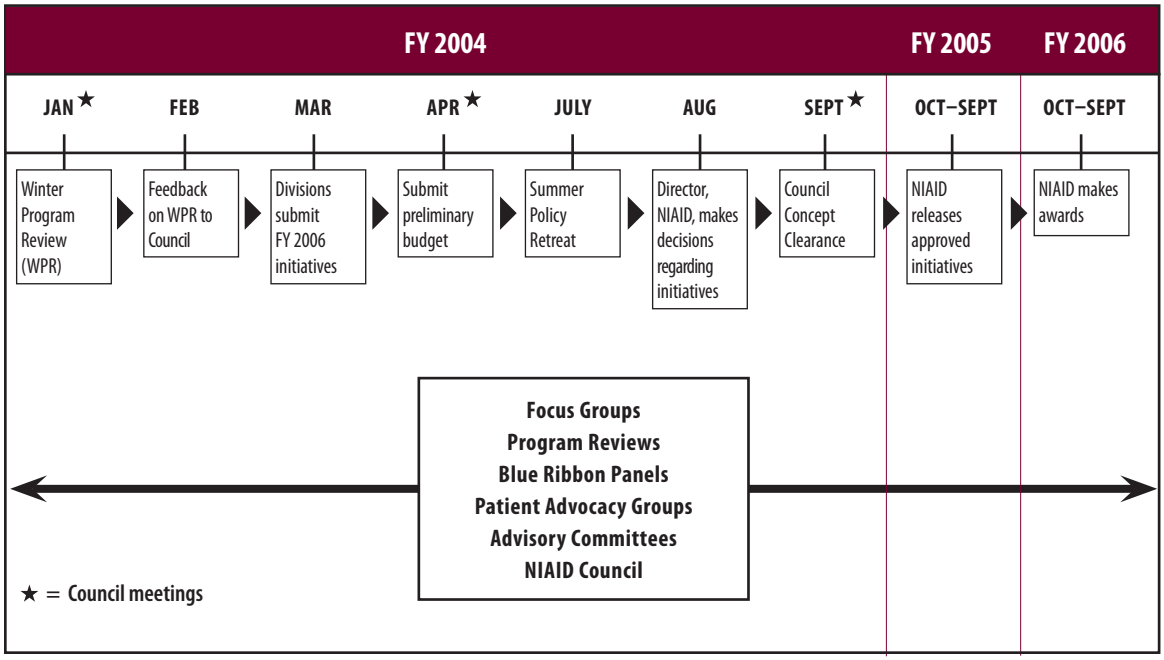
The strategic plans emphasize basic research on microbes; host defense mechanisms; and the development of drugs, diagnostics, and vaccines. The biodefense research agendas articulate immediate and longer term goals for research on Category A pathogens, which include smallpox, anthrax, Ebola virus, plague, botulinum toxin, tularemia, Marburg virus, Rift Valley fever, and Lassa virus; and goals for research on Category B and C priority pathogens. The research agendas also address the research resources, facilities, and scientific manpower needed to conduct basic and applied research in these areas. The strategic plan and research agenda for radiological and nuclear threats focuses on medical countermeasures to assess, diagnose, and treat civilians exposed to radiation, and mitigate the harmful effects of such exposure to the greatest extent possible. The strategic plans, research agendas, and progress reports can be accessed at *www.niaid.nih.gov/publications/bioterrorism.htm*.

Tremendous progress has been made since these reports were first released. NIAID has increased the breadth and depth of biodefense research and has made progress in meeting the specific goals of the Blue Ribbon Panel. The *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report* describes the progress made toward addressing the immediate goals outlined in the research agenda and can be accessed at *www2.niaid.nih.gov/biodefense/research/category_a_Progress_Report.pdf.* The *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens Progress Report* describes the progress made toward goals outlined in its corresponding strategic plan, and can be accessed at *www3.niaid.nih.gov/Biodefense/Research/strat_plan.htm*.

Another important strategic planning effort focuses on how to further stimulate research activities to address health disparities. The *NIAID Strategic Plan for Addressing Health Disparities*

articulates specific action plans for reducing disparities through (1) research on HIV/AIDS, transplantation, autoimmune diseases, tuberculosis, hepatitis C virus, and sexually transmitted diseases; (2) support for research infrastructure and research training; and (3) support for community outreach projects. The full text of the health disparities strategic plan can be accessed at *http://www.niaid.nih.gov/healthdisparities/NIAID_HD_PLAN_Final.pdf.*

NIAID PRIORITY-SETTING PROCESS



DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) was established in 1986 to help end the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of the human immunodeficiency virus (HIV), supporting the development of therapies for HIV infection and its complications and co-infections, and supporting the development of vaccines and other prevention strategies. To accomplish this, DAIDS plans, implements, manages, and evaluates programs in fundamental basic research; discovery and development of therapies and treatment strategies for HIV infection and its complications and co-infections; and discovery and development of vaccines, topical microbicides, and other prevention strategies. Staffed by over 130 employees, DAIDS comprises three main scientific programs—the Basic Sciences Program, the Vaccine and Prevention Research Program, and the Therapeutics Research Program.

Scientific Areas of Focus

Basic Research

HIV pathogenesis research increases understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission. HIV pathogenesis research also supports studies of how the immune system responds to the virus. Epidemiologic and natural history research provide information about the biology and clinical course of HIV in human populations, which enhances understanding of risk factors associated with HIV transmission and progression to AIDS. Knowledge gained from these studies helps researchers develop new agents and vaccines to combat HIV infection.

Currently, DAIDS is studying the natural history of HIV progression in men and women through several cohort studies. The Women's Interagency HIV Study is a collaborative, multisite, longitudinal study designed to investigate the impact of HIV infection on women in the United States (*http://statepiaps.jhsph.edu/wihs*). The Multicenter AIDS Cohort Study (MACS) is an ongoing study of the natural history of HIV infection in homosexual men (*http://statepi.jhsph.edu.macs.html*). The MACS began in 1983 and was able to capture information about a large number of men who seroconverted while enrolled in the study. DAIDS awarded the "Tri-Service AIDS Clinical Consortium Data Analysis and Coordinating Center (TACC/DACC)" contract in late 2005. The contractor will support the TACC, a multisite natural history study of HIV infection in active duty U.S. military personnel, by providing expertise that optimizes analyses of the cohort data and fully utilizes the network of TACC clinical sites, laboratories, and specimen repositories. NIAID is also cosponsoring a new program, the Pediatric HIV/AIDS Cohort Study (PHACS), in partnership with the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, and the National Institute of Mental Health. The objective of PHACS is to address continuing critical research questions on the clinical course of perinatally acquired HIV infection in adolescents and the consequences of fetal and neonatal exposure to antiretroviral chemotherapy in a representative cohort of children from the United States. The PHACS Leadership Group was awarded this year with funding for specific protocols slated for FY 2006.

DAIDS also supports a large portfolio of investigator-initiated grants in HIV pathogenesis for a variety of areas, including mechanisms of viral entry, evasion, and replication; structure, function, and mechanism of action of viral genes and proteins; roles of cellular accessory molecules in replication; immunologic and virologic events controlling primary infection and formation of

latent reservoirs; development of *in vitro* and *ex vivo* assays to monitor virus growth, immune responses, and reservoir status during HIV disease; animal models; and genetic analysis of host factors that modulate viral infection or disease progression. These grants serve as a source of new knowledge that fuels the discovery of new drugs and vaccine concepts.

To further stimulate the pursuit of new ideas, DAIDS funds a number of targeted programs. The Novel HIV Therapeutics: Integrated Preclinical/Clinical Program is an example of how DAIDS supports the discovery, development, and evaluation of innovative HIV treatment concepts through multidisciplinary research and formal corporate partnering. The Centers for AIDS Research program, also supported by DAIDS, provides administrative and resource support and emphasizes the importance of translational research and collaborations between basic and clinical investigators.

To assist the research community and promote collaborative studies, NIAID supports the NIH AIDS Research and Reference Reagent Program, which is now in its 18th year of operation. The Reagent Program continues to provide the scientific community worldwide with a critical and unique resource of state-of-the-art biologics and chemicals useful for HIV research.

The Division's basic research efforts have yielded significant scientific information about the basic biology of HIV and the immune response to HIV infection. For example, DAIDS-funded investigators have identified the critical steps of how HIV uses the host cell machinery to enter and exit the cell, as well as the existence of multiple, persistent HIV reservoirs despite treatment with highly active antiretroviral therapy (HAART). In response, researchers are focusing their efforts on identifying new strategies to understand and eliminate these reservoirs of latent HIV. Research has also identified genetic markers that influence progression to AIDS. Although much has been learned in recent years, questions still remain about the molecular interactions involved in the regulation of HIV expression and replication and why the host immune response is not fully effective in controlling the infection. Information about how the virus attacks the body and how the body defends itself is critical to providing additional targets against which therapeutic interventions and vaccines can be directed.

Therapeutics

In order to foster the development of new HIV therapies, DAIDS supports research on potential new cellular and viral therapeutic targets, as well as new approaches to validate existing targets. The areas of research include identifying molecules that could effectively block HIV replication and control infection, improved formulations of existing agents, approaches to enhance or restore the immune system of HIV-infected individuals, molecular and genetic approaches to protect susceptible uninfected cells, combination regimens that impede the emergence of viral resistance, and assays to measure restored immunity of HIV-infected individuals. Clinical studies help determine which new agents are effective against HIV and its associated complications and co-infections, and also clarify how best to use these drugs. Investigations include basic research and drug discovery, preclinical development of candidate therapeutics, and advanced clinical testing in humans.

The evaluation of new drugs and therapeutic agents in people is a critical aspect of therapeutic research. Clinical studies define new agents that are effective against HIV and its associated opportunistic infections and co-infections and clarify how best to use these drugs. As such, DAIDS supports clinical therapeutic research in adults and children through several large clinical trials networks, including the Adult AIDS Clinical Trials Group (*www.aactg.org*), the Pediatric AIDS Clinical Trials Group (*http://pactg.s-3.com*), the Terry Beirn Community Programs for

Clinical Research on AIDS (*www.cpcra.org*), and the Acute Infection and Early Disease Research Program (*http://www.aiedrp.org*).

DAIDS-sponsored therapeutics research already has had a dramatic impact on understanding the pathogenesis and clinical management of HIV infection over the past decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped define national and international guidelines for the treatment of primary HIV infection and associated opportunistic infections and co-infections, as well as prophylactic regimens for these secondary infections; (2) identified biological and genetic markers such as CD4+ counts and viral load for predicting a drug's effectiveness and disease progression; and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-child transmission (MTCT) of HIV.

More recent studies have shown that HAART regimens, including reverse transcriptase and potent protease inhibitors, are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance or noncompliance with complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. Thus, there is an ongoing, urgent need for new therapeutic agents and regimens, new ways to boost immunity, and methods to rebuild and replace immunity lost to HIV infection. In addition, DAIDS is developing strategies to address critical questions regarding the long-term effects of antiretroviral therapy, development of drug resistance, and the most optimal approaches to medical management, especially to prevent MTCT.

Vaccine and Prevention Research

The discovery and development of an HIV/AIDS vaccine to prevent HIV infection is a high priority at NIAID. Through a balanced HIV program that integrates both basic research and empiric testing of candidate vaccines, NIAID supports a broad spectrum of research and development on HIV/AIDS vaccines. Preclinical vaccine research and development examines new vaccine concepts and approaches, as well as new ways to deliver HIV antigens in order to safely induce a potent anti-HIV immune response. Studies using animal models are aimed at defining the safety, immunogenicity, and efficacy with which the vaccine protects the host.

Clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-HIV response in people. NIAID-supported clinical trials of preventive HIV vaccines are carried out in the HIV Vaccine Trials Network (HVTN) (*www.hvtn.org*). HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. Started in 2000, it has made progress towards its goal of developing and conducting a comprehensive HIV vaccine clinical research agenda that addresses scientific and public health needs and builds on scientific opportunities in the field of HIV vaccine research. HVTN has undergone significant expansion to support international trials, instituted highly functioning protocol development teams, developed new vaccine concepts and advanced new protocols, reorganized laboratory programs, and developed an extensive training program. (Additional HVTN information is located in the "Vaccine Research and Development" section on page 138.)

Vaccine research and development are supported through an extensive portfolio of investigator-initiated research in basic virology, immunology, and microbiology. Several DAIDS programs also support the interface of preclinical and clinical research. These resources stimulate the development of new vaccine concepts and ensure a rational, deliberate process for moving concepts

into and through clinical trials. Among the vaccine research programs supported by DAIDS that encourage development along various stages of the vaccine pipeline are the Innovation Grant Program for Approaches in HIV Vaccine Research Program, which encourages novel and innovative concepts in vaccine discovery and development; the HIV Vaccine Research and Design Program, which supports concepts that have evolved beyond early testing and "matured" innovation grants; and the Integrated Preclinical/Clinical AIDS Vaccine Development Program, which supports the iterative processes of vaccine concept refinement and testing. Through this program, researchers investigate promising vaccine concepts that are amenable to product development and are likely to lead to preliminary studies in humans.

In addition, HIV Vaccine Design and Development Teams, consisting of consortia of scientists from industry and/or academia, identify specific promising vaccine concepts amenable to targeted development. In response to recommendations by the Global HIV Vaccine Enterprise, in 2005, NIAID created a Center for HIV/AIDS Vaccine Immunology (CHAVI), a virtual center that will link a large group of domestic and international scientists to elucidate the correlates of immune protection against HIV and use that knowledge to design a vaccine to elicit those specific immune responses. Funded through a U01 cooperative agreement mechanism, CHAVI will support an intensive, multi-resourced, coordinated, consortium approach to address key scientific roadblocks to HIV vaccine development and to design, develop, and test novel HIV vaccine candidates, as defined by NIH and as identified by the strategic plan of the Global HIV Vaccine Enterprise. The CHAVI team is expected to be a highly collaborative, cooperative, and interactive team of leading researchers who will devote the majority of their time to the application of state-of-the-art immunological tools.

NIAID also supports comprehensive research on other non-vaccine, biomedical/behavioral prevention approaches, including the prevention of MTCT of HIV; topical microbicides; interventions such as community education and counseling that reduce behaviors such as drug abuse and unsafe sex, which expose people to HIV; programs to reduce intravenous drug abuse; measures to control other sexually transmitted infections (STIs); and antiretroviral therapies that could reduce the spread of HIV from infected people to their partners.

Non-vaccine HIV prevention research is conducted primarily through the HIV Prevention Trials Network (HPTN) (*www.hptn.org*). The HPTN, formed in 2000 with additional support from the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse, is a global, multicenter network dedicated to non-vaccine prevention research. Additional HPTN information is located in the "AIDS" section on page 45.

NIAID supports several research programs to facilitate the development of microbicides, including the Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM). This program is designed to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The IPCP-HTM now supports nine multi-project microbicide development efforts for novel single and combination microbicides. These efforts include pilot phase I clinical trials that support the development and evaluation of new technologies for determining microbicide safety as well as the optimization of newly identified microbicide candidates. In addition, the Microbicide Design and Development Teams (MDDT) program is designed to engage industry in the streamlined development of microbicide candidates, emphasizing combination products with multiple active agents. One award was made in FY 2005, with additional awards expected

in FY 2006, and an expansion of the program planned for FY 2007. NIAID, in coordination with the NIH Office of AIDS Research, is also developing a new microbicide research program to foster the translation of microbicide innovations to preclinical development. This novel milestone-driven program, designated the Microbicide Innovation Program, is designed to identify innovative concepts and discoveries relevant to topical microbicides and then, through a phased program of support, provide the rationale and evidence needed to determine their merit in advancing along the development path.

The Division's comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. NIAID-supported researchers have designed new vaccine strategies, modified viral antigens and vaccine vectors to improve the elicited immune response, further explained the envelope structure of HIV, advanced understanding of the role of antibody and cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes, developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies will address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. In other prevention research, new microbicides will be evaluated for their safety, acceptability, and ability to prevent the sexual transmission of HIV. Moreover, building on past research that identified an inexpensive regimen to reduce HIV transmission at birth, NIAID will continue to evaluate other practical regimens for preventing MTCT of HIV, especially during breastfeeding.

Lastly, because the majority of new infections are occurring in the developing world, NIAID's prevention and treatment research activities are conducted on a global scale. In FY 2001, NIAID launched the Comprehensive International Program of Research on AIDS (CIPRA). CIPRA provides long-term support directly to developing countries to plan and implement a comprehensive HIV/AIDS prevention and research agenda relevant to their populations and to strengthen the infrastructure required to carry out this research. Currently, there are three R03 grants, three U01 cooperative agreements, and five U19 cooperative agreements being funded through the CIPRA program in the following countries: Cambodia, China, Haiti, Malaysia, Peru, Russia, Senegal, South Africa, Thailand, and Vietnam. For more information, visit the Web site at *www.niaid.nih.gov/daids/cipra*.

Expanding Global Research Activities

With the growing global impact of HIV/AIDS, there is a critical need for cost-effective prevention and treatment strategies in limited-resource regions of the world where more than 95 percent of HIV infections occur. With the explosive growth of new infections in the developing world, most of DAIDS-funded clinical research programs now have an international component. DAIDS supports research at academic and medical research centers, and collaborates with research and development companies worldwide. Many DAIDS activities support countries listed in the President's Emergency Plan for HIV/AIDS Relief, which include Cote d'Ivoire, Botswana, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia. While domestic research continues to focus on identifying the most effective treatment and prevention options for adults, adolescents, and children, internationally focused activities are designed to define global research priorities, ensure the clinical relevance of future vaccine

and prevention strategies to human populations most in need, strengthen collaborations with local investigators worldwide, and support training and infrastructure development in developing countries.

In response to the changing HIV pandemic and to expand upon and better coordinate the global research activities, NIAID is restructuring all of its HIV clinical trials research networks. In addition to increasing collaboration, efficiency, and flexibility, the new structure is designed to encourage greater integration of vaccine, prevention, and treatment research to improve upon research efforts and to address high priority research questions, particularly in resource-limited settings, where AIDS is most devastating.

Advisory Groups

DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and training scientific investigators. As part of this process, DAIDS works with a number of advisory groups and community and health professional organizations to help evaluate and redirect the Division's global research programs by identifying research needs, setting priorities, and planning future programs. These advisory bodies include the Acquired Immunodeficiency Syndrome Research Review Committee (AIDSRCC), the AIDS Research Advisory Committee (ARAC) and the AIDS Vaccine Research Working Group (AVRWG). The AIDSRRC advises the Directors of the NIH and NIAID with respect to programs and activities in the areas of AIDS as well as the prevention and treatment of the major opportunistic infections associated with AIDS. The ARAC advises the Directors of DAIDS and NIAID on all aspects of the research portfolio, reviews progress and productivity of ongoing efforts, provides assistance in identifying critical gaps and obstacles to progress, and approves of concepts for new initiatives. The AVRWG assists in developing a comprehensive research program for expediting the discovery and development of an HIV vaccine. A listing of ARAC and AVRWG members is located in on pages 166 and 168, respectively.

Collaborations

DAIDS actively supports and promotes public- and private-sector alliances to maximize available research opportunities and resources. Its commitment to identify effective vaccine and prevention strategies and novel treatments has led to a steady increase in international activities, particularly in the developing world, where there is critical need for cost-effective prevention, treatment, and care. These efforts, in particular, necessitate collaboration with other Federal and non-Federal agencies, given the complexity of global research efforts. As a result, NIAID has forged collaborations with the Centers for Disease Control and Prevention (CDC) and Department of Defense (DoD) to bring together the vast expertise, experience, and resources of each organization and help foster coordination and efficiency. The Partnership for AIDS Vaccine Evaluation is one example of collaboration between NIAID, CDC, and DoD that was established as a way to accelerate global HIV vaccine research efforts and increase efficiency and cost effectiveness through shared laboratory capabilities, clinical trial sites, and compatibility of protocols and data. Another example is the Global HIV Vaccine Enterprise, created to foster collaboration, cooperation, and transparency in the conduct of HIV vaccine clinical trials on a global scale. The Enterprise consists of a conglomerate of international scientists and organizations committed to accelerating the development of preventive vaccines for HIV/AIDS.

Role of Community

DAIDS has long recognized the importance of sustained relationships with the community, which are necessary to help foster and maintain trust and ensure that the research is designed to meet community needs. Each of the clinical research networks supported by DAIDS has

a Community Advisory Board (CAB) that works with the leadership of the network on all aspects of the research process, and other CABs that work with each individual research site. The CABs help ensure that the researchers are working in partnership with the community and help improve communications between the community and researchers. Community outreach and education are also integral components of the Division's activities. In addition, in 2001, NIAID launched its national campaign to stimulate and enhance the national dialogue concerning HIV preventive vaccines and to create a supportive environment for future vaccine studies. A steering group represents the diversity of communities affected by the AIDS pandemic and includes nationally recognized leaders in fields such as communications, the media, social marketing, community education and organizing, health care, advocacy, public policy, and HIV prevention. The campaign's activities include partnerships with national and local community groups, the development and provision of resources and materials, and advertisement and promotion of HIV Vaccine Awareness Day on May 18th of every year.

Major Programs Supported by DAIDS

- Acute Infection and Early Disease Research Program
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- Center for HIV/AIDS Vaccine Immunology
- HIV Prevention Trials Network
- HIV Vaccine Design and Development Teams
- HIV Vaccine Research and Design Program
- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Trials Network
- HIV Vaccine Communications Campaign
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Innovation Grants for AIDS Vaccines
- Integrated Preclinical/Clinical AIDS Vaccine Development Program
- Integrated Preclinical/Clinical Program for HIV Topical Microbicides
- Microbicide Design and Development Teams
- Microbicide Innovation Program
- Multicenter AIDS Cohort Study
- Pediatric AIDS Clinical Trials Group
- Pediatric HIV/AIDS Cohort Study
- Simian Vaccine Evaluation Units
- Terry Beirn Community Programs for Clinical Research on AIDS
- Women's Interagency HIV Study

DIVISION OF ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION

Mission

The human immune system is composed of intricate networks of specialized cells, molecules, and organs that act together to defend the body against foreign invaders such as viruses, bacteria, and fungi that can cause disease. However, aberrant immune responses play a critical role in the development of immune-mediated diseases, which include asthma and allergic diseases; autoimmune disorders; primary immunodeficiencies; and rejection of transplanted solid organs, tissues, and cells. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

The past two decades of focused research on the immune system have resulted in major advances in understanding the mechanisms that underlie a range of immune-mediated diseases. These advances in conceptual understanding now provide realistic opportunities for improvement in the diagnosis, treatment, and prevention of many of these diseases. The Division of Allergy, Immunology, and Transplantation (DAIT) (*www3.niaid.nih.gov/about/organization/dait/default.htm*) promotes and supports a broad range of basic, preclinical, and clinical research to enhance understandings of the causes and mechanisms that lead to the development of immunologic diseases and to generate an expanded knowledge base that can be applied to the development of improved measures of diagnosis, treatment, and prevention of immune-mediated diseases. The ultimate goal of DAIT's research program is the development of effective approaches for the treatment and prevention of immune-mediated diseases.

The Division supports research initiated by individual investigators; multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; clinical research programs to assess the safety and efficacy of new therapeutic approaches; and interdisciplinary cooperative research centers.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the treatment and prevention of transplant rejection, asthma and allergic diseases, and autoimmune diseases. Another area of program growth involves the application of emerging technologies to further understanding of immunologic principles and to develop diagnostic and prognostic tools and biomarkers of disease activity and therapeutic effect.

Scientific Areas of Focus

Asthma and Allergic Diseases

Asthma and allergic diseases are among the major causes of illness and disability in the United States. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses on the underlying immune mechanisms involved in these disorders and on approaches to improve diagnosis and treatment by fostering investigator-initiated projects and supporting cooperative clinical studies. In FY 2005, NIAID established the Food Allergy Research Consortium, a collaborative research program designed to develop new approaches to treat and prevent

food allergy. The consortium will conduct basic, clinical, and epidemiological studies, and develop educational programs aimed at parents, children, and healthcare providers. The Inner-City Asthma Consortium: Immunologic Approaches to Reduce Asthma Severity, a network of basic scientists and clinical investigators, was established by DAIT in FY 2002 to evaluate the efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. Current clinical trials include an Asthma Control Evaluation, the Urban Environment and Childhood Asthma protocol, and the Inner-City Anti-IgE Therapy for Asthma.

Autoimmune Diseases

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the U.S. population and disproportionately afflict women. DAIT supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease. DAIT supports the Autoimmunity Centers of Excellence, which conduct collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies and mechanism-of-action studies. DAIT also supports the Centers for Autoimmune Disease Prevention, which focus on advancing knowledge for the prevention of rheumatoid arthritis and other autoimmune diseases. The goal of the Autoimmunity Prevention Centers is to develop the knowledge base necessary to design preventive interventions that could be administered efficiently and safely. In FY 2005, the Prevention Centers supported 22 pilot projects to test innovative approaches that might lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression.

Basic and Clinical Immunology

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through this research provides the knowledge base necessary to develop treatment and prevention strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary program projects on the biology of the immune system, including the basic biology of immune responses for vaccine research, transplantation immunology and chronic rejection, and autoimmunity. Clinical immunology studies focus on immune-mediated diseases, including autoimmune diseases, asthma and allergic diseases, acute and chronic transplant rejection, and immunodeficiencies. Research in these clinical areas is supported by program projects on mucosal immunity, autoimmune diseases, and methods of immune intervention.

Immune Tolerance

Immune tolerance is a high priority for NIAID and, as part of a broad-based, long-range plan to accelerate research in this important area, DAIT established the Immune Tolerance Network (ITN). The ITN is an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases; asthma and allergic diseases; and rejection of transplanted organs, tissues, and cells. The goal of these therapies is to "re-educate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity

against infectious agents. The ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The ITN has established a variety of state-of-the-art core facilities and has supported 20 approved clinical protocols and several additional studies of the immune mechanisms that lead to development, maintenance, or loss of clinical tolerance. Currently, the ITN supports seven clinical trials in solid organ and islet transplantation and two cohort studies to better understand the immune mechanisms involved in the acquisition of spontaneous tolerance to organ grafts. More information about the ITN is available on its Web site at *www.immunetolerance.org*.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases are caused by intrinsic defects in the cells of the immune system and are often due to inherited genetic defects. NIAID-supported research focuses on understanding the causes and immune mechanisms leading to the development of primary immunodeficiency diseases. This includes identifying pathogenic gene mutations and other contributing etiologies; expanding the genetics knowledge base to improve diagnosis and facilitate genetic counseling and decisionmaking for affected individuals; and providing protective and curative treatments, including gene therapy. In FY 2003, NIAID, with cosponsorship from the National Institute for Child Health and Human Development, established the Primary Immunodeficiency Diseases Consortium. The consortium (1) provides leadership and mentoring; facilitates collaborations; enhances coordination of research efforts; and solicits, reviews, and makes awards for pilot or small research projects; (2) maintains a primary immunodeficiency diseases registry, which provides data to the research community about the clinical characteristics and prevalence of these diseases; and (3) develops a repository of specimens from subjects with primary immunodeficiency diseases. The consortium has funded 16 research proposals and continues to review 4 to 8 new proposals 3 times each year. Additional information on consortium activities is available on its Web site: *www.usidnet.org*. NIAID also supports research in large animal models of primary immunodeficiency diseases, as well as clinical trials to determine the most efficacious bone marrow transplantation regimens in patients with these diseases.

Transplantation

The Division's research in transplantation immunobiology is focused on understanding the mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells; developing preclinical models to evaluate promising therapies to prevent and treat graft rejection; conducting clinical trials of new therapeutic agents and approaches to improve graft survival and function; and understanding the pathogenesis of chronic graft failure and developing new treatments and preventive strategies. Clinical research to evaluate new therapeutic approaches to improve kidney engraftment and survival is carried out through the Cooperative Clinical Trial in Pediatric Kidney Transplantation. In FY 2005, NIAID and the National Heart, Lung and Blood Institute established Clinical Outcome of Live Organ Donors, a program of epidemiologic research focused on the medical and functional outcomes of individuals who have donated a kidney or a lobe of lung for transplantation into an individual with end-stage organ failure. This program supports a consortium consisting of multiple clinical transplant centers and a Data Coordinating Center.

Primary Research Areas

Asthma and Allergic Diseases

- Asthma and Allergic Diseases Research Centers
- Inner-City Asthma Consortium
- Food Allergy Research Consortium
- Immune System Development and the Genesis of Asthma
- Atopic Dermatitis and Vaccinia Immunization Network

Autoimmune Diseases

- Autoimmune Diseases Prevention Centers
- Autoimmunity Centers of Excellence

Basic and Clinical Immunology

- Cooperative Centers for Translational Research on Human Immunology and Biodefense
- Hyperaccelerated Award/Mechanisms in Immunomodulation Trials
- Large Scale Antibody and T Cell Epitope Discovery Program
- Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations
- Population Genetics Analysis Program: Immunity to Vaccines/Infections
- Emerging/Re-emerging Infectious Diseases
- Immune Epitope Database and Analysis Program
- Innate Immunity Receptors and Adjuvant Discovery

Immune Tolerance

- Immune Tolerance Network
- Innovative Grants on Immune Tolerance
- Nonhuman Primate Immune Tolerance Cooperative Study Group

Primary Immunodeficiency Diseases

- Primary Immunodeficiency Diseases Consortium

Transplantation

- Cooperative Clinical Trial in Pediatric Kidney Transplantation
- Clinical Trials in Organ Transplantation
- Genomics of Transplantation Cooperative Research Program
- Clinical Outcomes of Live Organ Donors
- Clinical Islet Transplantation Consortium

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

Mission

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually every human infectious agent (except HIV), including pathogens used as agents of bioterrorism. DMID supports a wide variety of projects spanning the spectrum from basic research through applied research, along with the development and clinical evaluation of new drugs, vaccines, and diagnostics. NIAID also funds projects to sequence the full genomes of medically important microbes, which can be exploited in many ways—for example, to trace microbial evolution, to locate targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

Research areas in basic bacteriology and mycology include molecular structure and function, genetics, biochemical composition, and physiologic and biochemical processes. Studies of these pathogens extend basic insights to identify vaccine candidate antigens and drug targets, and also describe mechanisms of infection, pathogenicity, and virulence. Areas of particular interest include anthrax, streptococci, pneumonia, nosocomial (hospital-acquired) infections, tularemia, fungal infections, antibiotic resistance, plague, bacterial sexually transmitted infections, botulinum toxin, and bacterial diarrheas.

Research areas in virology include molecular structure and function, genetics, synthesis, and mechanisms of viral reproduction; characterization of viral proteins and nucleic acids; mechanisms of pathogenicity, latency, persistence, and reactivation; interactions with immune systems; and vaccine development. Basic research information is being used to combat important viral diseases such as influenza, smallpox, herpes, congenital cytomegalovirus infection, viral hemorrhagic fevers, hepatitis, and viral diarrheas.

Research on parasites involves the application of biochemical, genetic, and immunologic approaches. Studies of parasites are leading to the identification of protective and diagnostic antigens, and to the development of more effective drugs. In addition, studies of arthropod vectors are aimed at controlling the transmission of important pathogens such as the malaria parasite.

One of the primary goals of the Division is to develop new and improved vaccines and strategies for vaccine delivery for the entire spectrum of infectious agents including bacteria, viruses, fungi, and parasites. Since 1981, DMID has supported a program for the accelerated development of new vaccines to direct advances in molecular biology, immunology, genetics, and epidemiology. An integral component of these efforts is vaccine safety, which is evaluated in every vaccine clinical trial sponsored by NIAID.

DMID also supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. Examples include diagnostic tests for sexually transmitted infections (STIs) and Lyme disease and the development of antimicrobial resistance markers.

Finally, DMID maintains a drug development program that supports research at three levels: drug discovery (accomplished by screening and by targeted molecular research), preclinical evaluation (in animal models of human infections), and clinical trials (evaluation of new therapies in humans).

Scientific Areas of Focus

Biodefense

As concern grows about the use of biological agents in acts of terrorism and war, federal agencies are evaluating and accelerating the development of countermeasures to protect the

public from the health consequences of such an attack. Our ability to detect and prevent infections that emerge as a result of bioterrorist incidents depends to a large degree on the state of biomedical science. Basic and applied research supported by the NIH complements the efforts of other federal agencies by developing the essential tools—diagnostics, therapeutics, and vaccines—that are needed by physicians, nurses, epidemiologists, and other public health workers to prevent and control outbreaks of disease. NIAID is the primary NIH Institute that supports and conducts research on the diagnosis, prevention, and treatment of infections caused by a wide variety of emerging pathogens, including those that could be intentionally introduced.

In response to the need for rapid development of resources for biodefense, NIAID continues to expand its research related to potential agents of bioterrorism as part of a broad research agenda involving other agencies within the Department of Health and Human Services and the Department of Defense. The components of the NIH's biodefense research program include the development of biodefense-relevant diagnostics, therapeutics, and vaccines, as well as genomics, basic research on potential agents of bioterrorism, and infrastructure to support advanced research. Recent NIAID programmatic accomplishments include support for bioinformatics and proteomic resource centers; expansion of the Vaccine and Treatment Evaluation Units to accommodate testing of vaccines such as those for smallpox and anthrax; development of several new animal models for diseases caused by NIAID Category A, B, and C agents; support for grants and public-private partnerships for early product development through clinical trials of biodefense vaccines and drugs; a centralized repository to acquire, authenticate, store, and distribute NIAID Category A, B, and C agents to the scientific community for use in research and product development; and the continued expansion of research capacity through the multimillion dollar Research Centers of Excellence and National and Regional Biocontainment Laboratories across the United States, which will provide critical resources for biodefense and emerging infectious disease research.

Emerging and Re-emerging Infectious Diseases

Emerging infectious diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence. Recent outbreaks of severe acute respiratory syndrome (SARS) and avian influenza in Asia and monkeypox in the United States are examples of emerging infectious diseases, whereas tuberculosis and pertussis are examples of diseases that have re-emerged after a period of decline. Factors involved in the emergence and re-emergence of infectious diseases include evolution of microbes; changes in compliance with vaccination guidelines; overuse of antimicrobials; and changes in the interactions between humans and the environment due to human population growth, density, and contact with animal vectors or animals that may serve as disease reservoirs.

Both emerging and re-emerging diseases have significant implications for domestic and global health. DMID supports a broad spectrum of basic research on infectious diseases, including studies of epidemiology; pathogenesis; transmission and microbiology of emerging infectious diseases; and applied and clinical studies to develop and test vaccines, diagnostics, and therapeutics for these diseases. Examples of DMID-supported research on emerging infectious diseases include robust research programs in influenza, SARS, West Nile virus, and Lyme disease. In 2003, DMID established multiple Research Centers of Excellence, and National and Regional Biocontainment Laboratories across the United States, where scientists will be able to safely conduct critical research on emerging infectious

diseases and NIAID Category A, B, and C priority agents.

Vaccine Research and Development

DMID supports an active program of basic and applied research for the accelerated development of new vaccines, taking advantage of advances in molecular biology, immunology, genetics, and epidemiology. Research conducted under this program contributes to the development of new vaccines for a wide variety of bacterial, viral, and parasitic diseases, including SARS, malaria, influenza, West Nile virus, herpes, pneumonia, and whooping cough. DMID also supports research to develop novel vaccine delivery methods, such as transcutaneous skin patches and nasal vaccines. Additionally, DMID supports a large national and international network for clinical trials of safety and efficacy of vaccines. Recent expansions of the network will allow more trials focused on specific populations and larger clinical trials, including those for biodefense vaccines. DMID's *The Jordan Report*, now in its 20th anniversary edition, is a unique resource developed by the Division to inform the public health community and the general public of recent developments and the state of the science in vaccine research. This report can be viewed online at *www.niaid.nih.gov/dmid/vaccines/jordan20*.

Antimicrobial Drug Resistance

Emergence of drug-resistant infectious agents is becoming an increasingly important public health concern. Rapid evolution of microbes and misuse of antibiotics are major contributors to the rising number of resistant pathogen strains. Tuberculosis (TB), gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat because of the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired infections. More than 70 percent of the bacteria that cause hospital-acquired infections are resistant to at least one of the drugs most commonly used to treat them (see the Centers for Disease Control and Prevention. *Campaign to Prevent Antimicrobial Resistance in Healthcare Settings* online at: *www.cdc.gov/drugresistance/healthcare/problem.htm*). Also, drug resistance that was almost exclusively hospital- or health care-associated is appearing and originating with increasing frequency in the community, such as community-acquired, methicillin-resistant *Staphylococcus aureus*. Many physicians are concerned that several bacterial infections soon might be untreatable with currently available drugs.

NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens, including antimicrobial resistance among the major health care-associated bacterial pathogens. Specifically, NIAID supports investigator-initiated research on the molecular mechanisms responsible for drug resistance, as well as research to develop and evaluate new or improved therapeutics for disease intervention and prevention. Studies on several key organisms of interest seek to define how bacterial pathogens acquire, maintain, and transfer antibiotic-resistant genes. In August 2004, NIAID held the second Summit on the State of Anti-Infective Development to address the important issue of antimicrobial availability and to help determine the best ways for NIAID to address the key needs. (See *http://www.niaid.nih.gov/dmid/meetings/anti_infective_mtg_2004.pdf* for more information about the 2004 summit.) More recently, NIH sponsored a study by the National Academy of Sciences to generate ideas for innovative research approaches that would contribute to the development of new antimicrobial therapeutics. The report resulting from this study, *Treating Infectious Diseases in a Microbial World,* suggests several promising new avenues of research that could revolutionize the field of antimicrobial/anti-infective development.

NIAID also continues to participate in an interagency task force for the development of public health strategies to address antimicrobial resistance. *A Public Health Action Plan to Combat Antimicrobial Resistance,* developed by the task force, describes issues, goals, and action items in surveillance, prevention and control, research, and product development, as well as a plan for interagency and industry coordination in addressing this critical health issue. The action plan is available online at *http://www.cdc.gov/drugresistance/actionplan*.

Global Health

Infectious diseases pose a major public health challenge not only in the United States, but worldwide. NIAID research is based on the view that we live in a global community; we cannot separate the health problems of the United States from those of the rest of the world. Thus, the Institute seeks to create more effective means to prevent, diagnose, and treat infectious diseases of international importance by improving vaccines, diagnostics, and therapeutics that can be used in the developing world. This requires addressing special scientific and logistical challenges, such as accessing endemic sites and populations.

Scientists studying genomics, microbial physiology, epidemiology, natural history, disease transmission and progression, and vector control all contribute to NIAID's efforts to tackle infectious diseases on a global scale. The Institute supports laboratory, field, and clinical research through disease-specific initiatives, investigator-initiated grants, and special programs, such as the International Collaborations in Infectious Diseases Research (ICIDR) and the Tropical Medicine Research Centers (TMRCs). Both ICIDR and TMRC programs cover a broad spectrum of infectious diseases including respiratory, enteric, viral, and parasitic, as well as emerging diseases and sexually transmitted infections. These programs establish collaborations between scientists from the United States and those in host countries to address problems paramount to local communities, expand the expertise of U.S. and foreign scientists, and strengthen the academic base of the host institution. NIAID also offers small research grants that are specially designed to provide an entry point for investigators in developing countries to get NIH funding.

TB and malaria are two components of NIAID's extensive global health research portfolio. Together, these two diseases account for tremendous morbidity and mortality throughout the world. NIAID's TB research includes studying basic biology of drug-resistant and nonresistant strains, disease progression, diagnostics, vaccines, therapeutics, epidemiology, and genomics. The NIAID Tuberculosis Research Unit supports an international, multidisciplinary team of collaborators to translate basic research findings into the development of clinically useful products. Current research activities sponsored by NIAID for malaria include drug development, pathogenesis research, vaccine development, epidemiology, and vector control, as well as the Malaria Research and Reference Reagent Resource (MR4) Center, a repository that supports malaria research throughout the world.

Sexually Transmitted Infections

Sexually transmitted infections are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with HIV/AIDS. Scientists now believe that people who have STIs are at an increased risk of contracting HIV/AIDS. DMID's STI research emphasis is on vaccine development, as well as clinical, epidemiologic, and behavioral investigations directed toward strategies for primary and secondary prevention of STIs and conditions associated with having STIs, including pelvic inflammatory disease, infertility, tubal pregnancy, cervical cancer, fetal wastage, premature birth, congenital infection, and the spread of HIV.

NIAID supports individual investigator-initiated research grants and a variety of research programs for the development of more effective prevention and treatment approaches to control STIs. Research efforts include developing and licensing vaccines, topical microbicides, and treatments for STIs; understanding the long-term health impacts of sexually transmitted pathogens in various populations; stimulating basic research on the pathogenesis, immunity, and structural biology of these pathogens; and developing better and more rapid diagnostics. Specific programs supported by NIAID include the Sexually Transmitted Disease Cooperative Research Centers, which bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. Another program, the STI Clinical Trials Unit, conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STIs. Finally, the Topical Microbicides Program supports basic research, product development, and clinical evaluation activities aimed at developing female-controlled barrier methods for the prevention of STIs and HIV/AIDS infection.

Pathogen Genomics

In 1995, the first microbe-sequencing project, *Haemophilus influenzae* (a bacterium causing upper respiratory infection), was completed with a speed that stunned scientists. Encouraged by the success of this initial effort, researchers have continued to sequence an astonishing array of other medically important microbes. NIAID has made a significant investment in large-scale sequencing projects and projects to sequence the full genomes of many human pathogens, including those that cause tuberculosis, anthrax, plague, gonorrhea, chlamydia, cholera, pneumonia, aspergillosis, malaria, and influenza. In addition, NIAID collaborated with other funding agencies to sequence larger genomes of pathogenic fungi, protozoan pathogens such as the organism causing malaria, and invertebrate vectors of infectious diseases.

The availability of microbial and human DNA sequencing in publicly accessible databases has opened up new opportunities and allowed scientists to conduct functional analyses of genes and proteins in whole genomes and cells, as well as studies of the host immune response and an individual's genetic susceptibility to pathogens. When scientists identify microbial genes that play a role in disease, it paves the way to design drugs to block the activities controlled by those genes. Because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins, or to design candidate vaccines based on the proteins. Comparative genomic analysis of microbes also can be used to study the spread of a virulent or drug-resistant form of a pathogen.

NIAID is committed to continuing its support for projects to sequence the genomes of microbes, as well as increasing its support for functional genomics and proteomics, decoding sequence information, and determining its functional sequence. Moreover, NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community and to supporting the development of bioinformatic and computational tools and databases to allow investigators to have easy access to sequence and functional data for the functional genomic analysis of microbial pathogens. In summary, DMID supports a breadth of research activities on a variety of pathogens important in basic microbiology and infectious diseases.

DIVISION OF INTRAMURAL RESEARCH

Mission

The Division of Intramural Research (DIR) *(www3.niaid.nih.gov/about/organization/dir/default.htm)* conducts laboratory and clinical research covering a wide range of biomedical disciplines related to infectious diseases, immunology, and allergy. DIR scientists conduct basic laboratory investigations to understand the biology and genetics of the viruses, bacteria, protozoa, and other microbes that cause infectious diseases, as well as the ticks, mosquitoes, fleas, and flies that transmit them. They also study the multitude of cells, antibodies, proteins, and chemicals that compose the immune system. A fundamental understanding of the immune system is key to the development of therapies and vaccines for infectious diseases, and to deciphering and treating immunological disorders ranging from mild allergies to life-threatening immunodeficiencies.

DIR expertise is being applied to meet the challenge of emerging infectious diseases, such as avian influenza and West Nile fever, and to develop defensive measures against bioterrorism. In FY 2005, the DIR's long-term investments in viral vaccine development and poxvirus research paid important dividends, as vaccines for pandemic influenza and West Nile fever and diagnostics and therapeutics for smallpox progressed to advanced stages of development.

In addition, the DIR has a large program focused on investigations of prion diseases, such as "mad cow" disease and chronic wasting disease of deer and elk, which are caused by a transmissible agent that has little in common with conventional infectious microbes.

The ultimate goal of the Division's research is to contribute to the development of new and improved therapies, diagnostics, and vaccines that will improve health, save lives, and enhance the quality of life of people in the United States and throughout the world. This contribution might take the form of delineating a cell-signaling pathway, discovering the function of a tick gene, determining the three-dimensional structure of an immune cell receptor, or finding the enzyme malfunction causing a primary immunodeficiency disease.

Beyond the Laboratory

Though investigator-initiated basic research continues to be the mainstay of the NIH intramural program, today greater emphasis is being placed on translating laboratory research findings to the clinical arena. On the NIH campus, this is accomplished through the facilities of the NIH Clinical Center, the world's largest clinical research complex. There, physician-scientists treat patients with a variety of diseases, including AIDS, host defense defects, asthma, various parasitic diseases, and disorders of inflammation. NIAID currently has more than 80 active clinical protocols, under which patients participate in studies of new and promising treatments or diagnostic procedures, often derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the stimulating scientific setting of the NIH while they participate in DIR's basic and clinical research programs.

The DIR and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

Scientific Resources

Each of the 18 DIR laboratories (*http://www3.niaid.nih.gov/about/organization/dir/lab_des.htm)* has project-specific resources that are augmented by the expertise and services provided to all DIR labs by supporting branches. The DIR branches offer access to state-of-the-art technologies for peptide synthesis, protein sequencing, mass spectroscopy analysis of peptides and small molecules, electron microscopy, confocal microscopy, flow cytometry and cell sorting, yeast 2-hybrid screening, and DNA microarray analysis. The branches also provide genetically modified (transgenic as well as knockout/knockin) mice, extensive inhouse animal breeding and holding facilities (including nonhuman primates), oversight of animal protocols, and support to scientists conducting animal studies. Animal care facilities, including biosafety level (BSL)-3 facilities, are maintained in Bethesda, MD, and at DIR laboratories in Hamilton, MT. New facilities featuring animal BSL-3 and maximum containment BSL-4 labs are under construction, with completion scheduled for early 2006 and 2007, respectively. In addition to the facilities directly managed by NIAID, DIR investigators have access to NIH-wide facilities such as the Mouse Imaging Facility.

A multidisciplinary initiative begun in 2005 aims to use a systems biology approach to develop new computer modeling and simulation resources for immunology research. This initiative will integrate knowledge about the individual genes, molecules, and cells of the immune system into a coherent whole to provide a more global understanding of physiologic function. Interdisciplinary teams of mathematicians, engineers, computer experts, biophysicists, biochemists, geneticists, and cell biologists will provide the tools and techniques necessary for quantitative, predictive modeling of immune function in particular and biological systems in general.

This scientific teamwork is made possible by up-to-the-minute computer systems and communications resources. Computer linkages for DIR scientists include a local area network within NIAID and a wide area network linking DIR scientists in Bethesda, Rockville, and Frederick, MD, and the Rocky Mountain Laboratories in Hamilton, MT, to other NIH resources such as the National Library of Medicine. Teleconferencing equipment and direct satellite uplinks further enhance communications between DIR staff members and their colleagues across the campus and around the world. Investigators wishing to interact directly with other scientists in a focused setting can do so by joining one of the more than 80 NIH scientific interest groups organized around specialty areas.

Scientific Areas of Focus

Immunology Research

Immunology research is inextricably linked to studies of infectious diseases and allergy. In studying immunologic diseases, DIR scientists consider both the normal processes of the immune system and how these processes malfunction in the disease state. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system to recognize and destroy invading organisms. Second, the findings enhance the understanding and development of effective treatments for immunodeficiency diseases in which the immune cells are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Advances in immunology research in FY 2005 include:

- Discovery of the mechanisms by which caspase-8 deficiency causes both autoimmunity and combined immunodeficiency;
- Identification of *Toxoplasma* profilin as the first chemically defined ligand for Toll-like receptor 11;

- Association of autoantibodies to interferon-gamma with severe disseminated mycobacteria infections; and
- Precise identification of natural killer cells in nonhuman primates.

Allergy Research

Researchers studying allergic diseases concentrate on asthma; allergic reactions involving the skin, nasal passages, and sinuses; and chronic food allergy. Much of this research focuses on mast cells, which play an important role in many allergic disorders and secrete chemicals such as histamine. Histamine is responsible, in part, for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. Accomplishments in FY 2005 include the following:

- Opening of a pediatric allergy clinic to provide a focal point for translational research conducted in collaboration with NIAID intramural laboratories;
- Determination that a molecule called GATA-3 is a key factor in allergic diseases and a rational target for new drugs to treat allergies and asthma; and
- Initiation of a clinical study to gather clinical and immunological data to characterize allergic disease onset, progression, and remittance.

Infectious Disease and Biodefense Research

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing understandings of pathogenic organisms, host response to infection, vector biology, and chemotherapeutics. Studies of the microorganisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, West Nile fever, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the pathogen that are necessary for reproduction. Host studies can define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies can reveal new targets for public health interventions. Application of this multidisciplinary approach to investigations of new and re-emerging infectious diseases and biodefense research is a top DIR priority. DIR scientists are collaborating with colleagues from government, academia, and industry to develop vaccines, diagnostics, and therapeutics for high-priority pathogens and to conduct the basic laboratory research that provides the foundation for product development. In addition, DIR scientists are engaged in collaborative research in a number of developing countries with a high infectious disease burden. Additional information about DIR studies of biodefense research and emerging infectious diseases can be found on pages 61 and 84, respectively. Accomplishments in 2005 include the following:

- Identification of a pediatric respiratory syncytial virus vaccine candidate that is safe and stimulates a protective immune response in young infants;
- Development of the most potent anthrax neutralizing monoclonal antibodies reported to date;

- Discovery of how hemoglobin C protects against malaria; and
- Identification of a promising new target to fight certain hospital-acquired infections.

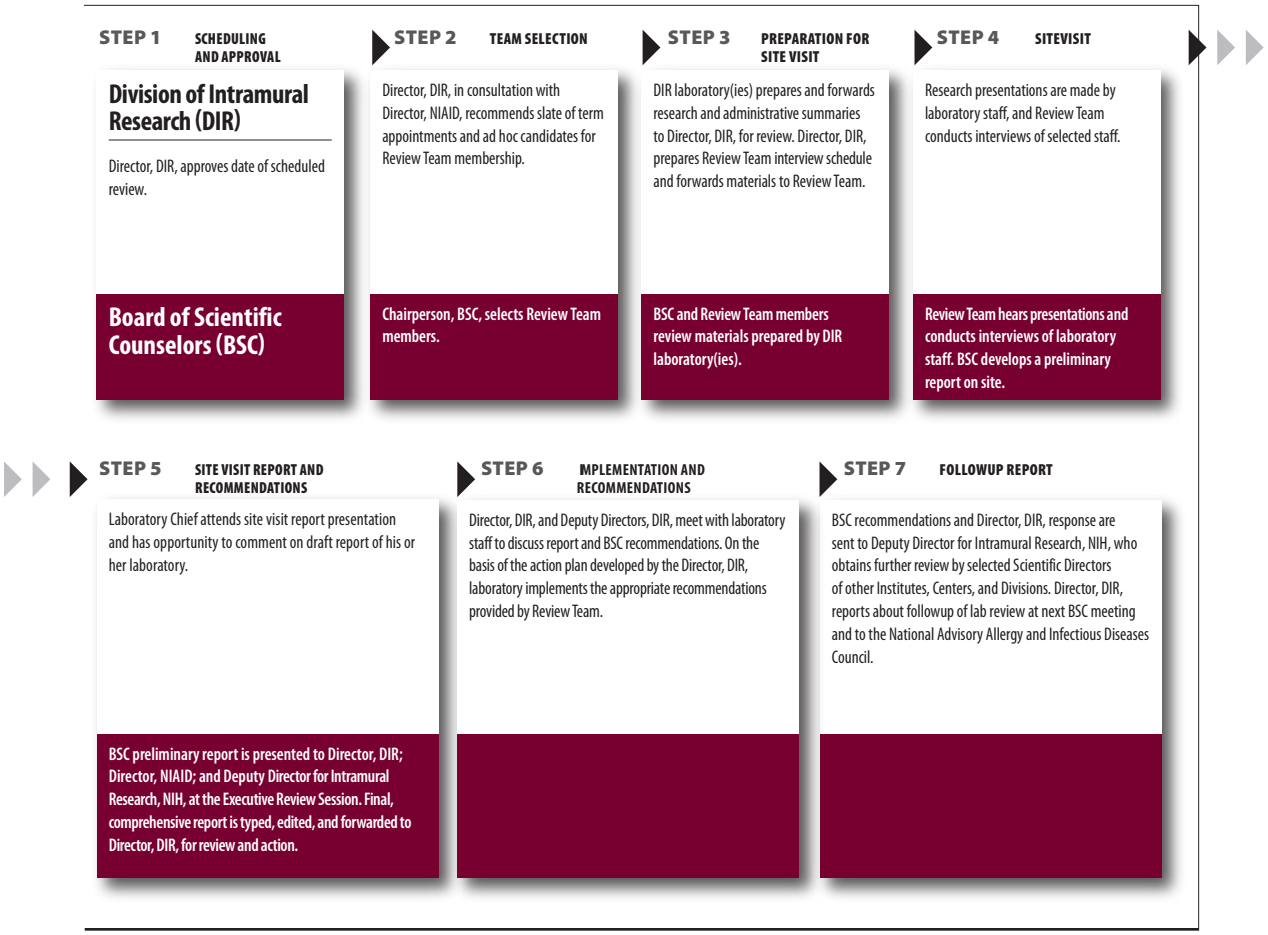
Vaccine Research

Candidate vaccines against many infectious agents of public health importance are undergoing laboratory and clinical testing in the DIR. These include vaccines for respiratory and gastrointestinal viruses, hepatitis viruses, and infectious agents that cause common tropical diseases such as malaria and dengue. DIR scientists also are collaborating in the development of vaccines to prevent the natural or deliberate spread of infectious diseases such as smallpox, severe acute respiratory syndrome (SARS), plague, and pandemic influenza. Studies are under way to develop vaccines against pathogenic flaviviruses such as the West Nile virus, St. Louis encephalitis virus, and tick-borne encephalitis virus. Investigations continue toward the development of a vaccine against the respiratory syncytial virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in the DIR. For accomplishments in 2005 and additional DIR information, see page 31.

Laboratory Review Process

The following chart provides information on the DIR's laboratory review process:

DIVISION OF INTRAMURAL RESEARCH LABORATORY REVIEW PROCESS



DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER

Mission

The Dale and Betty Bumpers Vaccine Research Center (VRC) (*http://www.niaid.nih.gov/vrc/default.htm*) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases. The primary focus of the VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. In 2005, 3.1 million people died from AIDS, and 4.9 million people were newly infected with HIV. Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond patients' financial reach. Therefore, effective, low-cost methods for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending the HIV epidemic.

To combat HIV, we now have at our disposal new information about the molecular and immunologic basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge may lead to new ideas and novel strategies for effective vaccines. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective HIV/AIDS vaccine. In this setting, VRC has a unique opportunity and responsibility to facilitate the translation of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

HIV strains worldwide display tremendous genetic diversity that might limit the protective immunity elicited by a single vaccine. Two types of HIV can be distinguished; these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside the region, whereas HIV-1 is the cause of the global pandemic. HIV-1 is further classified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit protective immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce effective immunity in a large percentage of those infected. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

Thus, the development of an effective vaccine against HIV is the primary mission of VRC. To this end, VRC collaborates closely with the NIAID Division of AIDS (DAIDS), particularly with regard to regulatory support and implementation of clinical trials through established trial networks. In addition to its research program for HIV/AIDS, VRC's research programs in biodefense have been expanded, intensified, and accelerated. For example, VRC, working closely with the NIAID Division of Microbiology and Infectious Diseases (DMID) and with industry partners, is positioned to make substantive contributions in the development of vaccines to protect against Category A and

B agents such as smallpox, West Nile virus, and hemorrhagic fever viruses (such as Ebola) that could pose a bioterrorist threat. VRC also is collaborating closely with DMID and the NIAID Division of Intramural Research to develop a vaccine for severe acute respiratory syndrome (SARS). In addition, VRC has recently accelerated its influenza vaccine development activities, and is developing gene-based vaccines using a prime-boost strategy against both annual and potential pandemic strains of influenza viruses.

Scientific Areas of Focus

Historically, the process of vaccine development can be characterized as empiric, guided more by trial and error with inactivated or attenuated organisms than by rational design that builds on basic concepts in immunology and virology. Although this development process has succeeded in generating vaccines to combat numerous important infectious agents, many diseases remain for which no vaccine exists. A new science of vaccinology that takes advantage of the latest technologies and scientific knowledge to design effective vaccines is now emerging. The VRC strategic plan is predicated on the belief that development of an effective AIDS vaccine will benefit from a thorough understanding of the basis of protective immunity to the virus and the mechanisms by which HIV evades immune surveillance.

The VRC process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, has been established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis, molecular biology, and structural biology with clinical trials methodology. Encompassing these activities at a single center possessing the capacity for vaccine production, VRC is working to advance the science of vaccine development.

The same infrastructure being employed to develop an effective HIV vaccine also is being deployed in the search for an improved smallpox vaccine, novel influenza vaccines, and for effective vaccines against Ebola, West Nile virus, and SARS.

Basic Research

Acquired Immunodeficiency Syndrome

The VRC aims to develop vaccine candidates that will induce effective humoral responses (immune protection offered by antibodies) and cellular immune responses (immune protection offered by direct action of immune system cells). Data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the assumption that both cellular and humoral immunity are factors in preventing HIV infection or controlling HIV disease, the VRC preclinical research program explores basic science questions relevant to vaccine design.

The VRC program in virus structural biology explores the rational design of vaccines that can induce potent virus-neutralizing antibodies. Using innovative crystallographic techniques, the structure of gp120, an important viral protein on HIV's surface, has been determined at the atomic level, leading to the identification and visualization of numerous overlapping mechanisms of immune evasion. VRC is using this and other structure-based analyses and protein-based principles to assist in the rational development of novel candidate vaccines for HIV. This approach also is being applied to the development of vaccines against other pathogenic viruses of public concern.

Development of candidate vaccines focuses on using portions of engineered HIV genes to express specific HIV proteins capable of triggering a protective immune response. These genes can be delivered by immunizing with either DNA or viral vectors. In DNA immunization, the host is immunized by direct administration of viral genes. Viral vectors also can be constructed. These viral vectors transport one or more HIV genes and cause infected cells to produce HIV-specific proteins. Rodent and primate models can be used to evaluate the safety, immunogenicity (induction of immune response), and degree of protection provided by these candidate vaccines.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens (substances causing an immune response) that elicit protective immunity against HIV is guided by studies that systematically evaluate the humoral and cellular immune responses generated by vaccine candidates. The development of reproducible, validated assays to measure T cell function and virus particle reduction is key to successful evaluation of both animal studies and human clinical trials. The VRC Immunology Core Laboratory is currently designing, optimizing, and performing immunologic assays that measure cellular and humoral immune responses. Candidate vaccines are being evaluated by intracellular cytokine staining, ELISPOT assays, and measurements of neutralizing and binding antibodies. VRC also is expanding current assays to be applicable to more antigens and various clades of HIV, as well as exploring ways to optimize and automate assay performance using state-of-the-art technologies in robotics.

By using these emerging technologies, scientists can determine how effectively a candidate vaccine protects against infection or disease.

Preclinical studies in small animals and primates are used to evaluate vaccine dose, formulation, and delivery route and to address the immunogenicity of multigene vectors and vaccine combinations. The accumulated knowledge from these preclinical studies is being used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing is integrated closely with VRC basic science and clinical programs to provide information on the advancement of promising candidate vaccines into human trials.

Scientists Study Previously Unobserved Characteristics of Acute HIV Infection. Chronic HIV infection is characterized by a steady but generally slow loss of CD4+ T cells (of both naïve and memory types). It has recently been shown that acute infection is accompanied by significant depletion of CD4+ T cells in mucosal tissues. Using a simian immunodeficiency virus (SIV) infection model, VRC scientists have shown that acute SIV infection is associated with very high rates of infection and depletion of memory CD4+ cells in multiple tissues. Extensive loss of memory CD4+ cells occurs not only from mucosal tissue but also from lymph tissue and peripheral blood. This demonstration of massive early loss of CD4+ memory T cells, an extraordinarily high loss of 24–48 percent of all memory CD4+ T cells within the first 2 weeks of infection, has critical implications for vaccine development and interventional therapies. Preventive and therapeutic strategies must be designed to prevent early and massive destruction of the memory CD4+ cell phenotype by reducing viral load during the acute phase of infection.

Identifying How HIV Escapes the Body's Defenses. One of the factors that underlies the inability to suppress HIV replication in infected individuals is that the virus mutates so rapidly that it is able to evade the T cell immune responses against it. This phenomenon, known as "immune escape," is thought to compromise the efficacy of vaccines designed to prevent infection by priming such T cell immune responses.

VRC scientists examined the breadth of T cell repertoire, i.e., the variety of T cells that make up the cellular immune response to the AIDS virus. These researchers showed that T cell responses that are narrow in their repertoire cannot tolerate viral mutations and allow the virus to escape rapidly. Conversely, T cell responses that have a broad repertoire seem more able to tolerate mutations and thus can contain the virus more easily. These considerations are extremely important in helping to establish a framework on which to base rational design of HIV vaccines.

New Studies Identify Mechanisms that Explain Patterns of Viral Transmission and Antibody Resistance. Dendritic cells (DCs) normally circulate throughout tissues and lymphoid organs, where they capture antigens and process them for presentation to the immune system. DCs also capture both CCR5- and CXCR4-tropic viruses efficiently and transmit them to T cells. The envelope (Env) glycoprotein of human immunodeficiency virus type 1 (HIV-1) (gp120) is highly glycosylated, and virus attachment to DCs is mediated largely through the mannose-specific C-type lectin receptor, DC-SIGN. VRC scientists have defined a mechanism to explain preferential transmission of CCR5-tropic viruses and have shown that, although immunoglobulin G neutralizing antibodies can block CCR5-tropic HIV-1 entry into myeloid DCs, once the virus is internalized through DC-SIGN by the antigen-presenting cell, it provides a previously unrecognized mechanism of immune evasion to neutralizing antibodies that might also be integral to HIV spread and persistence. The enhancement of infection and the protection from neutralizing antibodies provided by the DCs help the virus to efficiently infect host T cells. Inactivation of HIV-1 by neutralizing antibodies at the time of initial exposure would provide a potent mechanism to inhibit HIV infection *in vivo* and would be a desirable feature of an immune response elicited by a highly effective AIDS vaccine. The enhancement of infection and the protection from neutralizing antibodies provided by the DCs help the virus to efficiently infect host T cells. The ability of CCR5-tropic viruses to infect immature DCs allows the development of a reservoir of infected myeloid (m) DCs that infect T cells efficiently upon maturation. Preferential infection of immature mDCs by CCR5-tropic virus could serve as a cellular "Trojan horse" that initiates a persistent infection. Preferential infection of immature mDCs by CCR5-tropic virus can thus establish a pool of infected cells that can efficiently transfer virus at the same time that they protect the virus from antibody neutralization.

Ebola and Other Viral Hemorrhagic Fevers

Outbreaks of Ebola in Africa kill up to 90 percent of those infected. No effective treatment exists for this highly infectious disease, which causes extensive internal bleeding and rapid death. Vaccination is regarded as the best strategy for preventing or containing this deadly infection. Investigators at VRC, with scientific collaborators at the U.S. Army Medical Research Institute of Infectious Diseases, have developed a potentially effective vaccine strategy for blocking Ebola virus infection in nonhuman primates. Previous VRC studies showed that a combination of DNA vaccination and boosting with adenoviral (ADV) vectors that encode viral proteins protected cynomolgus macaques against Ebola virus challenge and generated cellular and humoral immunity.

West Nile Virus

VRC is currently developing a DNA-based vaccine against WNV in collaboration with the San Diego-based biotechnology company, Vical, Inc. The vaccine is based on an existing codon modified gene-based DNA plasmid vaccine platform designed to express WNV proteins and is being currently tested in a phase I clinical trial.

SARS

In response to the recent global outbreak of SARS, VRC investigators began work immediately on

the development of a potential vaccine. The VRC contracted with Vical, Inc. to manufacture a single closed, circular DNA plasmid-based vaccine encoding the S protein of SARS-coronavirus (CoV). VRC mouse studies demonstrated that this vaccine induces T cell and neutralizing antibody responses, as well as protective immunity. A phase I open-label clinical study to evaluate safety, tolerability, and immune response was initiated in FY 2005. The study enrolled 10 healthy 18–50 years old subjects, and administered 4 mg DNA vaccinations at three 1-month intervals. Interim study results indicate that the vaccine is well tolerated and the study is expected to be complete early in FY 2006.

Studies Shed Light on Important Genetic Differences in SARS Viruses. Immune protection against SARS-CoV infection has been conferred by vaccination directed toward the S glycoprotein, and this effect is mediated by humoral immunity. The evolving molecular heterogeneity of SARS-CoV has raised concerns about the breadth and efficacy of protection with specific vaccine strains and the possible development of immune escape. Molecular characterization of SARS viruses has revealed significant genetic differences among isolates but the functional consequences of these differences are not well understood. VRC scientists have now demonstrated that genetic variances account for several important functional differences, such as affinity for specific viral receptors and sensitivity to antibody neutralization. These results raise concerns about the ability of SARS vaccines to contain the spectrum of SARS-CoV isolates in nature and highlight the need to develop approaches that control these genetically diverse viruses.

Influenza

The VRC is exploring new approaches using novel technologies to develop a gene-based vaccine protective against influenza.

Gene-based Vaccination Might Provide Protective Immunity Against Diverse Influenza Viruses. Current influenza vaccines elicit antibodies effective against specific strains of the virus, but new strategies are urgently needed for protection against unexpected strains. DNA vaccines have been shown to provide protection in animals against diverse virus strains but the potency of the vaccines needs improvement. VRC scientists tested a DNA prime-recombinant adenoviral boost vaccine targeted at one of the influenza viral proteins, nucleoprotein (NP). Strong antibody and T cell responses were induced. Protection against viral challenge was substantially more potent than DNA vaccination alone. Importantly, vaccination protected against lethal challenge with highly pathogenic H5N1 virus. Thus, gene-based vaccination with NP might contribute to protective immunity against diverse influenza viruses through its ability to stimulate cellular immunity.

Clinical and Regulatory Infrastructure

The VRC has assembled a full clinical research support team consisting of physicians, study coordinators, nurse practitioners, research nurses, and recruitment and outreach specialists. These staff members represent VRC at community events, screen potential volunteers, and perform vaccinations and subsequent followup and testing of enrolled volunteers. The VRC also has developed the strong regulatory infrastructure required to support the development and testing of vaccines. In collaboration with DAIDS and DMID, VRC staff members manage the submission of Investigational New Drug (IND) applications to the Food and Drug Administration (FDA), develop protocols for human clinical trials, and ensure that all studies are performed in accordance with FDA guidelines, while meeting all applicable reporting requirements.

Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. Although animal models are invaluable for guiding the development of vaccine approaches in general, and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I and II studies in humans are required to validate safety and immunogenicity findings, and only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, VRC combines traditional empirical vaccine development with hypothesis-driven basic and preclinical research. In addition to traditional phase I studies in HIV seronegative volunteers, the VRC has been studying the ability of vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4+ and CD8+ immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will clarify mechanisms of cellular immunity and T cell memory that play a role in protection against HIV. Such data then can be applied to the development of therapeutic and preventive vaccines. To date, the VRC has conducted or collaborated with clinical networks on 19 human clinical trials.

The VRC actively collaborates with both intramural and extramural scientists and facilitates the movement of ideas from the broader community into clinical trials. Close ties are maintained with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale and international trials is already established. The VRC also maintains several strong collaborations with industry and academic partners with expertise in various areas such as DNA and viral vector production, vaccine devices and delivery, preclinical testing, and vector construction. When products emerge with promise for licensure, VRC will continue to interact with the pharmaceutical industry, which has a large capacity for and experience in product development and distribution.

Acquired Immunodeficiency Syndrome

The VRC's prime-boost strategy using a multigene, multiclade DNA plasmid vector prime, adenoviral vector (ADV) boost has progressed through phase I clinical trials and has entered into phase II trials. The two vaccines (six-plasmid DNA and four-vector ADV) developed by the VRC incorporate HIV genetic material from clades A, B and C, which cause about 90 percent of all HIV infections around the world. These are the first multigene, multiclade HIV vaccines to reach phase II clinical trials, marking an important milestone in the search for a single vaccine strategy that targets U.S. subtypes of HIV as well as clades causing the global epidemic. In phase I studies of the separate components, the vaccines were well tolerated and elicited cellular and humoral responses. A recently launched trio of trials (phase I/II) of this prime-boost strategy, sponsored by DAIDS, is being conducted by three international networks, the HVTN, International AIDS Vaccine Initiative, and U.S. Military HIV Research Program, to test the safety and immunogenicity of the prime-boost strategy in the Americas, Southern Africa, and Eastern Africa.

Ebola

In November 2003, the VRC initiated the first human trial of a vaccine designed to prevent Ebola infection. All injections for the study are complete and have been well tolerated. In addition to testing preventive vaccine candidates, the VRC is currently developing a vaccine that might be useful in an acute outbreak setting. For example, a recently tested candidate (a single vector ADV-only) vaccine elicited protective immunity in monkeys after a 4-week post-vaccination challenge, in contrast to previous 10-week or 6-month vaccine regimens. A second-

generation product that would provide coverage for Marburg and possibly Lassa virus might also be evaluated.

MVA

VRC is currently testing modified vaccinia Ankara (MVA) as an attenuated poxvirus with the potential to protect against vaccinia (the virus used to vaccinate against smallpox) or variola (the virus that causes smallpox). The vaccine was provided by Therion Biologics Corporation as part of a collaboration with the VRC. Two phase I clinical trials testing MVA as a component of a safer smallpox vaccine in both vaccinia-naïve and vaccinia-immune populations have recently concluded, and data will be used by NIAID to guide the design of other studies to further the development of safer smallpox vaccines.

New Initiatives

NIAID has recently developed a NIAID Vaccine Immune T-cell and Antibody Laboratory (NVITAL), in Gaithersburg, MD. This new facility will perform validated immunological assays in support of phase II/III clinical studies and product licensure, and will serve as a Good Labor Practices (GLP) resource for centralized immunogenicity testing across different NIAID-sponsored vaccine projects. It is planned that this facility will support immunological analysis activities for the VRC's recently initiated phase II international HIV vaccine studies.

The VRC has constructed a contractor-leased and contractor-operated Vaccine Pilot Plant (VPP) that will manage production of multiple vaccine candidates originating from VRC. The VPP will function in concert with the Vaccine Production Laboratory located at the Bethesda campus to transfer new vaccine technology for pilot-scale production of vaccine material for use in clinical trials. The VPP, completed in late 2005, is a self-contained facility of 126,900 square feet with the capacity to produce four to eight clinical lots of vaccine annually.

Human Clinical Trials and Licensure of an AIDS Vaccine

VRC is working closely with its scientific collaborators and with FDA to discuss the potential for expedited approval of candidate AIDS vaccines. The carefully considered use of surrogate endpoints (i.e., measures of the vaccine's ability to provoke an immune response) in AIDS vaccine trials could substantially accelerate the licensure of an effective AIDS vaccine. Clinical information validating the use of surrogate endpoints can accrue from well-designed trials, and this information can be applied to the design of future trials.

DIVISION OF EXTRAMURAL ACTIVITIES

Organizational Overview

The Division of Extramural Activities (DEA) (*http://www3.niaid.nih.gov/about/organization/dea/default.htm*) serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts, managing NIAID's research training and international programs, and conducting initial peer review for funding mechanisms with Institute-specific needs.

In addition to providing broad policy guidance to Institute management, DEA also oversees NIAID's chartered committees, including the National Advisory Allergy and Infectious Diseases Council; disseminates information to its extramural community through its large Internet site and publications; and conducts extramural staff training and communications through the NIAID intranet.

DEA staff members interact intensively with grantees, contractors, reviewers, Council members, applicants, and staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome; the Division of Allergy, Immunology, and Transplantation; and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch (GMB) issues all NIAID grant awards after negotiating the terms of the award with grantees. GMB specialists determine award amounts, develop administrative terms and conditions, and release official award documents. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowed and how to formulate a budget for an application. GMB specialists supervise the day-to-day administration and financial management of Institute grants and cooperative agreements, while ensuring that grants comply with existing policies.

The Contract Management Program (CMP) (*www.niaid.nih.gov/contract*) manages the administrative aspects of NIAID's research and development contract portfolio. CMP specialists help develop requests for proposals, negotiate technical and business aspects of proposals, and select proposals for funding. Contract specialists are well versed in legal, technical, business, and cost-related topics, including Federal Acquisition Regulations. They provide investigators with guidance on changes in the scope of the research, the use of funds, and other administrative issues.

The Scientific Review Program conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications (RFAs) and requests for proposals (RFPs). Scientific review administrators assist NIAID staff members with the design, development, and review of initiatives. They also conduct initiative phasing, perform quality control of RFAs and RFPs, and formulate peer review strategies.

The Referral and Program Analysis Branch (RPAB) handles receipt and referral for grant applications that undergo initial review at NIAID. RPAB also performs scientific classification and data analysis of NIAID-funded grants, contracts, and intramural research projects for official scientific information reports.

Several offices and staff members in the DEA Office of the Director (OD) play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including innovative electronic systems. In addition, the OD is a long-time leader in

developing innovative technologies that have been adopted by the NIH, including electronic peer review and acquisition systems.

- The Office of Special Populations and Research Training (OSPRT) (*www3.niaid.nih.gov/about/organization/dea/osprtpage.htm*) manages and awards fellowships (F), institutional training (T), and research career (K) grants. OSPRT provides oversight and coordination for NIAID's minority and women's health activities and initiatives, and manages research supplements for underrepresented minorities and scientists with disabilities.

- The Office for Innovation and Special Programs (*www3.niaid.nih.gov/about/organization/dea/oisp.htm*) manages grants for NIAID's small business programs—Small Business Innovation Research and Small Business Technology Transfer.

- The Office of International Extramural Activities (*www3.niaid.nih.gov/about/organization/dea/oiea.htm*) helps develop policies for international applicants and grantees. It reviews the financial systems of non-U.S. grantees and communicates with other Federal agencies about international polices for select agents.

- The Office of Knowledge Resources (OKR) (*www3.niaid.nih.gov/about/organization/dea/okr.htm*) informs the Institute and its extramural research community of funding opportunities, advice, policy updates, and other news. OKR provides budget and payline information as well as tutorials on NIH operations, planning and writing grant applications, and managing grant awards. The newsletter, NIAID Funding News (*www.niaid.nih.gov/ncn/newsletters/default.htm*), and the NIAID Research Funding Web site (*www3.niaid.nih.gov/researchfunding*) are designed for the extramural research community, while the newsletters, NIAID Insider (*intra.niaid.nih.gov/organization/dea/DEA%20Express/index.html*) and Inside Extramural (*intra.niaid.nih.gov/Organization/DEA/DEA%20Express/2006/enl021706.htm*), are tailored to Institute staff.

- The Committee Management Office (*www3.niaid.nih.gov/about/organization/dea/cmo.htm*) oversees the legal and policy requirements for NIAID's chartered committees, which include the NAAIDC, the Board of Scientific Counselors, the AIDS Research Advisory Committee, and special emphasis panels. It also administers Scientific Review and Evaluation Awards.

- The Office of Data Quality and Initiative Development (*www3.niaid.nih.gov/about/organization/dea/odqid.htm*) initiates, plans, designs, and oversees extramural research initiatives. It also performs review and quality control of solicited grant and contract initiatives.

- The Office of Scientific Resource Development (OSRD) (*www3.niaid.nih.gov/about/organization/dea/osrd.htm*) develops Web-based and classroom training for NIAID staff and expands Institute learning resources. It educates NIAID staff on key scientific, clinical, and management mechanisms to enhance job performance.

- The Office of Program Coordination and Operations (*www3.niaid.nih.gov/about/organization/dea/opco.htm*) manages NIAID initiative phasing plans, develops NIAID Council guidance and timetables, manages the grants records center, and works with the administrative office to manage daily functional activities.